

PATENT SPECIFICATION

NO DRAWINGS

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L148,622

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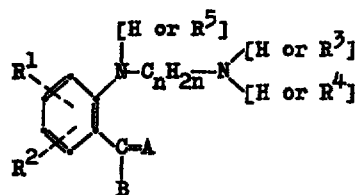
COMPLETE SPECIFICATION

Novel Diamines and the Manufacture thereof

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel diamines and the manufacture thereof.

The novel diamines provided by the invention are compounds of the general formula



(I)

wherein A represents an oxygen atom or an =NH, =N—OH or =N-(lower alkyl) group, B represents a pyridyl, phenyl, halo-phenyl, trifluoromethyl - phenyl, nitro - phenyl, (lower alkyl) - phenyl, (lower alkylamino) - phenyl or (lower alkoxy) - phenyl group, R¹ and R² each represent a halogen atom or the trifluoromethyl, nitro or amino group or a

lower - alkyl or lower - alkoxy group, R³ and R⁴ each represent a lower - alkyl group or R³ and R⁴ taken together with the nitrogen atom to which they are attached represent a five-membered or six-membered heterocyclic ring which can optionally contain an oxygen atom or a further nitrogen atom [which latter atom may carry as a substituent a lower - alkyl, hydroxy - (lower alkyl), (lower alkoxy) - (lower alkyl) or (lower alkenyloxy) - (lower alkyl group)], R⁵ represents a lower - alkyl or lower - alkenyl group and C_nH_{2n} represents an alkylene group having two carbon atoms between the two nitrogen atoms) and wherein the broken lines denote that the substituents attached thereby are optional, and acid addition salts thereof.

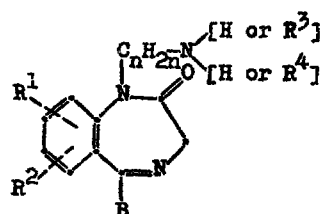
The compounds of formula I hereinbefore and their pharmaceutically-acceptable acid addition salts are characterised by an antidepressant action on the central nervous system and are useful not only in the relief of symptoms associated with depression of the central nervous system, but also in the prevention and reversal of central nervous system depression caused by exogenous chemical agents. They may be used as medicaments in the form of pharmaceutical preparations which contain them in admixture with a compatible pharmaceutical carrier; for example, a compatible organic or inorganic, solid or liquid carrier suitable for enteral (e.g. oral) or parenteral administration. For making up the preparations there may be employed inert substances such as water, gelatin, lactose, starches,

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- magnesium stearate, talc, vegetable oils, gums, polyalkyleneglycols, petroleum jelly or any other compatible carrier useful for the preparation of medicaments. The pharmaceutical preparations may be made up in solid form (for example, as tablets, dragées, suppositories or capsules) or in liquid form for example, as solutions, emulsions or suspensions. If desired, the pharmaceutical preparations may be sterilized and/or may contain auxiliary substances such as preserving agents, stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain other therapeutically useful substances. In preparations for administration to a warm-blooded animal, there is present from about 0.1 mg to 100 mg (preferably from about 0.1 mg to 30 mg and more preferably from about 0.2 mg to 10 mg) of active amine per kilogram of body weight of the said animal.
- The term 'lower alkyl' is used in this specification to mean a straight-chain or branched-chain alkyl group containing from 1 to 7 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl and butyl). The term 'halogen' is used to mean bromine, chlorine, iodine and fluorine. The term 'lower alkoxy' designates a straight-chain or branched-chain alkoxy group containing from 1 to 7 carbon atoms (e.g. methoxy, ethoxy and isopropoxy). The term 'lower alkenyl' denotes a straight-chain or branched-chain alkenyl group containing from 2 to 7 carbon atoms such as allyl. The grouping $-C_nH_{2n}-$ includes straight-chain and branched-chain alkylene groups such as trimethylene, tetramethylene, pentamethylene, 1-methyl - propylene, 2-methyl - propylene, 1-methyl - butylene and 3,3-dimethyl - propylene. The symbols R^3 and R^4 , subject to the foregoing proviso, can be absent or can represent straight-chain or branched-chain alkyl groups containing from 1 to 7 carbon atoms such as methyl, ethyl, propyl, isopropyl and butyl. Thus, $-N(H \text{ or } R^3)$ (H or R^4) can represent an amino, lower alkyl-amino or di(lower alkyl)-amine group. Further, R^3 and R^4 taken together with the nitrogen atom to which they are attached can form a five-membered or six-membered heteromonocyclic ring, preferably a 1-piperazinyl, piperidino, 1-pyrrolidinyl or morpholino group. The heterocyclic ring may contain an oxygen atom or a further nitrogen atom and this latter atom may carry, as a substituent, a straight-chain or branched-chain lower-alkyl group such as methyl, ethyl and isopropyl, a hydroxy - (lower alkyl) group such as hydroxy - ethyl, a (lower alkenyloxy) - (lower alkyl) group such as vinyloxy - alkyl groups or a (lower alkoxy) - (lower alkyl) group such as ethoxy - ethyl. Examples of saturated five-membered or six-membered heterocyclic groups represented by $-N(R^3)$ (R^4) are piperidino((lower alkyl) - piperidino, (lower alkoxy) - piperidino, 1 - pyrrolidinyl, (lower alkyl) - 1 - pyrrolidinyl, (lower alkoxy) - 1 - pyrrolidinyl, morpholino, (lower alkyl) - 1 - piperazinyl, hydroxy - (lower alkyl) - 1 - piperazinyl, (lower alkenyloxy - alkyl) - 1 - piperazinyl, (lower alkoxy - alkyl) - 1 - piperazinyl and 1 - piperazinyl. Thus, the said heteromonocyclic ring contains five or six members in the ring and is preferably saturated.
- Interesting classes of diamines provided by the present invention comprise the following:
- compounds of formula I in which B represents a pyridyl, phenyl, halo-phenyl, trifluoromethyl - phenyl, nitro - phenyl, (lower alkyl) - phenyl or (lower alkoxy) - phenyl group, and acid addition salts thereof.
 - compounds of formula I in which B represents a pyridyl, phenyl, halo-phenyl, trifluoromethyl - phenyl, nitro - phenyl, (lower alkyl) - phenyl or (lower alkoxy) - phenyl group, R^3 and R^4 are both absent and n stands for 3, 4, 5, 6, or 7, and acid addition salts thereof,
 - compounds of formula I in which R^4 is present, R^3 is absent and C_nH_{2n} stands for a propylene group, and acid addition salts thereof,
 - compounds of formula I in which R^5 is absent and B represents a 2 - (lower alkyl-amino) - phenyl group, and acid addition salts thereof,
 - compounds of formula I in which R^4 is present, R^3 is absent and C_nH_{2n} stands for an ethylene or 2 - (C_1-C_5 alkyl) - ethylene group, and acid addition salts thereof,
 - compounds of formula I in which R^4 is present, R^3 and R^5 are absent and C_nH_{2n} stands for an ethylene or 2 - (C_1-C_5 alkyl) - ethylene group, and acid addition salts thereof, and
 - compounds of formula I in which C_nH_{2n} stands for an ethylene or 2 - (C_1-C_5 alkyl) - ethylene group and B represents a 2 - (lower alkylamino) - phenyl group, and acid addition salts thereof. The preferred diamines provided by the invention are those compounds of formula I in which R^1 is absent and R^2 is present in the 5-position (that is to say, in the *para*-position to the anilino nitrogen atom) and represents a halogen atom (particularly a chlorine atom), and acid addition salts thereof. Furthermore, when B represents a pyridyl group, it is preferred that this is a pyridyl - (2) or pyridyl - (4) group. Especially preferred compounds of formula I are the 5 - halo - 2 - [N 1 [3 - di(lower alkyl) amino - propyl] - amino] - 2' - fluoro - benzophenones, the 5 - halo - 2 - [N - [3 - di(lower alkyl) amino - propyl] - amino] - benzophenones and the 5 - nitro - 2 - [N - [3 - di(lower alkyl) amino - propyl] - amino] - benzophenones.
- The novel diamines provided by the inven-

tion are manufactured, also in accordance with the invention, in various ways.

Thus, according to one process provided by the invention, the novel diamines aforesaid are manufactured by hydrolysing a benz-
 5 diaz[1,4]epine of the general formula



(II)

wherein B, R¹, R², R³, R⁴, n and the broken lines have the significance given earlier, with
 10 an acid in the presence of an inert organic solvent, and, where required, introducing the group R³ by lower-alkylation or lower-alkenylation, introducing the group(s) R³ and/or R⁴
 15 by lower-alkylation, converting the resulting product in which A represents an oxygen atom into a corresponding product in which A represents an =NH, =N—OH or =N—(lower alkyl) group by treatment with ammonia,
 20 hydroxyl amine or a lower-alkyl amine as the case may require, converting any fluoro-phenyl group B into a (lower alkylamino)-phenyl group, hydrolysing any imine product with a strong acid and/or converting any product into an acid addition salt.

25 Many of the benzdiaz[1,4]epine starting materials of formula II are claimed *per se* in the specifications of our Letters Patent Nos. 1,040,548, 1,051,795, 1,077,358 and 1,098,242. Interesting classes of benzdiaz-
 30 [1,4]epine starting materials of formula II are the following:

a) those in which B represents a pyridyl, phenyl, halo-phenyl, (particularly 2-fluoro-phenyl), trifluoromethyl-phenyl, nitro-phenyl,
 35 (lower alkyl)-phenyl or (lower alkoxy)-phenyl group,

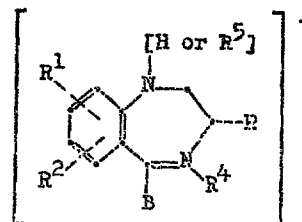
b) those in which R⁴ is present and C_nH_{2n} stands for a propylene chain and

c) those in which R³ is absent, R⁴ is present and C_nH_{2n} stands for an ethylene or 2 - (C₁—C₃ alkyl) - ethylene group. Preferred
 40 benzdiaz[1,4]epine starting materials of formula II are those in which R¹ is absent and R² is present in the 7-position and represents a halogen atom (particularly a chlorine atom). Especially preferred benzdiaz[1,4] epine
 45 starting materials are the 7 - halo - 1 - [3 - di(lower alkyl)amino - propyl] - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - benzdiaz[1,4] - epinone - (2)s. The 7 -
 50 halo 1 - [3 - di(lower alkyl)amino - propyl] - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4] - epinone - (2)s and the 7 - nitro - 1 -

[3 - di(lower alkyl) - amino - propyl] - 5 - phenyl - 2,3 - dihydro - 1H - benz-
 55 diaz[1,4]-epinone - (2)s.

The hydrolysis of a benzdiaz[1,4]epine starting material of formula II is suitably carried out using mineral acids such as sulphuric acid, nitric acid, polyphosphoric acid or a hydrohalic acid (e.g. hydrochloric acid). The
 60 hydrolysis can be carried out at any temperature and pressure; for example, at room temperature and atmospheric pressure or at a temperature above or below room temperature. Advantageously, the hydrolysis is carried out
 65 at elevated temperatures. It is most preferred to carry out the hydrolysis at about the reflux temperature of the hydrolysis mixture. For example, if a benzdiaz[1,4]epine start-
 70 ing material in which C_nH_{2n} stands for a propylene group is hydrolysed with a mineral acid under the foregoing conditions there is obtained a compound of formula I in which
 75 C_nH_{2n} stands for a propylene group, R⁵ is absent and A represents an oxygen atom.

According to another process provided by the present invention, those novel diamines aforesaid in which C_nH_{2n} stands for an ethylene or 2 - (C₁—C₃ alkyl) - ethylene group,
 80 R⁴ is present and R³ (when present) represents a lower-alkyl group are manufactured by treating a quaternary salt containing a cation of the general formula



(III)

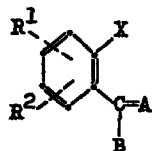
wherein B, R¹, R², R⁴, R⁵ and the broken lines have the significance given earlier and R represents a C₁—C₃ alkyl group, with a base under hydrolysing conditions and, where
 90 required, introducing the group R⁵ by lower-alkylation or lower-alkenylation, introducing the group R³ by lower-alkylation, converting the resulting product in which A represents an oxygen atom into a corresponding product in which A represents an =NH, =N—OH
 95 or =N—(lower alkyl) group by reaction with ammonia, hydroxyl amine or a lower-alkyl amine as the case may require converting any fluoro-phenyl group B into a (lower alkyl-amino)-phenyl group, hydrolysing any imine product with a strong acid and/or converting any product obtained into an acid addition salt.

Interesting classes of quaternary salts useful as starting materials for this process comprise the following:

- 5 a) those in which B represents a pyridyl, phenyl, halo-phenyl (particularly 2-fluorophenyl), trifluoromethyl-phenyl, nitro-phenyl, (lower alkyl)-phenyl or (lower alkoxy)-phenyl group and
- 10 b) those in which R⁵ is absent.
- Preferred quaternary salts are those in which R¹ is absent and R³ is present in the 7-position and represents a halogen atom (particularly a chlorine atom). Especially preferred quaternary salts are the 7 - halo - 5 - phenyl - 1,4 - dimethyl - 2,3 - dihydro - 1H - benz-
15 diaz[1,4] - epinium methosulphates.

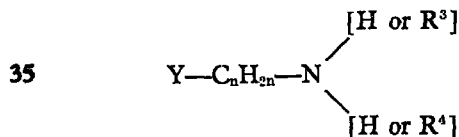
The treatment of a quaternary compound containing a cation of formula III hereinbefore is preferably carried out in an aqueous medium which may include an inert water-miscible organic solvent such as methanol or ethanol. The base may suitably be an alkali-metal hydroxide (e.g. sodium hydroxide) or an alkaline-earth-metal hydroxide, e.g. calcium hydroxide). The treatment can be carried out at any suitable temperature, but it is preferred to operate at temperatures below room temperature.

According to yet another process provided
20 by the invention, the novel diamines aforesaid are manufactured by reacting a compound of the general formula



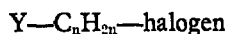
(IV)

either with a compound of the general formula



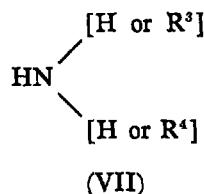
(V)

or with a compound of the general formula



(VI)

and treating the reaction product with a compound of the general formula



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and, in either case, splitting off any protecting group present and, where required, introducing the group R⁵ by lower-alkylation or lower-alkenylation, introducing R³ and/or R⁴ by lower-alkylation, converting any product in which A represents an oxygen atom into a corresponding product in which A represents an =NH, =N—OH or =N—(lower alkyl) group by treatment with ammonia, hydroxyl amine or a lower-alkyl amine as the case may require, converting any fluoro-phenyl group B into a (lower alkylamino)-phenyl group, hydrolysing any imine product with a strong acid and/or converting any product into an acid addition salt: A, B, R¹, R², R³, R⁴, R⁵, n and the broken lines having the significance given earlier and one of the symbols X and Y standing for a halogen atom and the other symbol standing for an amino, lower alkyl-amino, lower alkenyl-amino or protected-amino (e.g. tosyl-amino) group.

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Certain of the starting materials of formula IV are claimed *per se* in the specifications of our Letters Patent Nos. 972,971, 972,973, 972,975, 972,976 and 1,033,936. Interesting classes of starting materials of formula IV hereinbefore comprise the following:

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a) those in which B represents a pyridyl, phenyl, halo-phenyl (particularly 2-fluorophenyl), trifluoromethyl-phenyl, nitro-phenyl, (lower alkyl)-phenyl or (lower alkoxy)-phenyl group,

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b) those in which X stands for a protected-amino group (preferably a tosyl-amino group). The preferred starting materials of formula IV hereinbefore are those in which R¹ is absent and R² is present in the 5-position and represents a halogen atom (particularly a chlorine atom). Especially preferred intermediates of formula VIII hereinafter are the 5 - halo - 2 - [(3 - halo - propyl) - amino] - 2 - fluoro - benzophenones, the 5 - halo - 2 - [(3 - halo - propyl) - amino] - benzophenones and the 5 - nitro - 2 - [(3 - halo - propyl) - amino] - benzophenones. The preferred starting materials of formula V hereinbefore are those in which R⁴ is present and C_nH_{2n} represents a propylene group and those in which R⁴ is present, R³ is absent and C_nH_{2n} represents an ethylene or 2 - (C₁—C₅ alkyl) - ethylene group.

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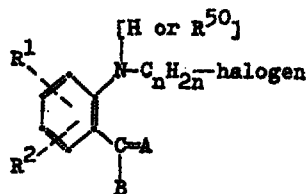
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According to one embodiment of the last-mentioned process, a compound of formula IV hereinbefore in which X stands for a halogen atom (preferably a chlorine, bromine or iodine atom) is reacted with a compound of formula V hereinbefore in which Y stands for

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an amino, lower alkyl-amino, lower alkenyl-amino or protected-amino group. According to a preferred aspect of this embodiment, the compound of formula IV is reacted with a compound of formula V in which R^3 and R^4 are absent and Y stands for an amino group (e.g. 1,3 - diamino - propane, 1,3 - diamino - 2 - methyl - propane or 1,3 - diamino - butane) to give a compound of formula I in which R^3 and R^4 are both absent. This preferred aspect is conveniently carried out at an elevated temperature (e.g. at a temperature above ca 75°C). The compound of formula V used in the preferred aspect can be present in an excess amount whereby it serves as the reaction medium. Alternatively, any conveniently available non-reactive organic solvent such as N,N - dimethyl - formamide, dimethyl sulphoxide, a lower or higher alkanol or an amine such as pyridine, picoline or quinoline can be used as the reaction medium.

According to another embodiment of the last-mentioned process, a compound of formula IV hereinbefore in which X represents an amino, lower alkyl-amino, lower alkenyl-amino or, preferably, a protected-amino group is reacted with a compound of formula VI hereinbefore in which Y stands for a halogen atom, the resulting compound of the general formula



(VIII)

wherein A, B, R^1 , R^2 , n and the broken lines have the significance given earlier and R^{50} represents a lower-alkyl, lower-alkenyl or protecting group, is treated with a compound of formula VII hereinbefore and any protecting group is split off from the resulting product. The treatment of a compound of formula VIII with a compound of formula VII is preferably carried out in the presence of an alkali (e.g. sodium hydroxide) and any suitable inert organic solvent. It will be appreciated that when ammonia is used as the compound of formula VII there is obtained a compound of formula I in which R^3 and R^4 are both absent. Further, when a lower-alkyl amine is used as the compound of formula VII there is obtained a compound of formula I in which one of R^3 and R^4 is present and the other is absent and when a di(lower alkyl) amine or heteromonocyclic amine is used as the compound of formula VII there is obtained a compound of formula I in which R^3 and R^4 are both present and

represent lower-alkyl groups which may be joined to form a heteromonocyclic ring as hereinbefore defined.

According to yet another embodiment of the last-mentioned process, a compound of formula IV hereinbefore in which X represents a protected-amino group is reacted with a compound of formula V hereinbefore in which Y represents a halogen atom and the protecting group is split off from the reaction product. According to a preferred aspect of this embodiment, a compound of formula IV in which X represents a tosyl-amino group is reacted with a compound of formula V in which Y represents a chlorine, bromine or iodine atom. This reaction is preferably carried out by converting the compound of formula IV into its sodio derivative at the nitrogen atom to which the tosyl group is attached (e.g. using sodium hydride or sodium methoxide) prior to reaction with the compound of formula V. A convenient and efficient method for removing the tosyl group is by heating in the presence of a suitable proton-donating acid agent such as sulphuric acid.

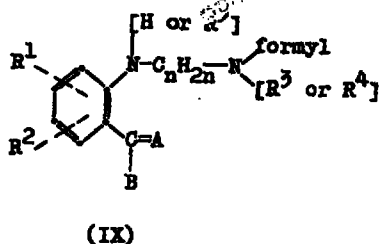
While a tosyl group is preferred as the protecting group in the last-mentioned process, it will of course be appreciated that any equivalent protecting group such as another aryl-sulphonyl group (e.g. benzene-sulphonyl) or a carboxylic acyl group (e.g. acetyl) can be present as the protecting group. Preferably, the protecting group is a carboxylic acyl group or the benzene-sulphonyl group or a derivative of the latter. However, all that is required of the protecting group is that it functions efficaciously in the reaction and can be readily split off when required.

Compounds of formula I hereinbefore in which R^5 is absent can be lower-alkylated or lower-alkenylated by a variety of methods to give the corresponding compounds in which R^5 is present. For example, compounds of formula I in which R^5 is absent can be reacted with an appropriate diazo-alkane (e.g. diazo-methane), di(lower alkyl) sulphate (e.g. dimethyl sulphate) (lower alkyl) halide (e.g. methyl iodide) or (lower alkenyl) halide (e.g. allyl bromide) in a medium such as ether, benzene, an alcohol (e.g. ethanol), N,N-dimethyl-formamide or dioxane.

Suitably, the reaction is carried out using sodium methoxide, sodium hydride or the like to form the sodio derivative at the anilino nitrogen atom and reacting the resulting sodio derivative with an equivalent amount or an excess of the appropriate alkylating or alkenylating agent.

Compounds of formula I hereinbefore in which R^3 and/or R^4 is absent can be mono(lower alkylated) or di(lower alkylated). The n - mono(lower alkyl) compounds can be manufactured by heating a compound of formula I in which R^3 and R^4 are absent under reflux with ethyl formate to yield the N-

formyl derivative thereof. The resulting N-formyl derivative is then heated under reflux with sodium hydride and, for example, a lower-alkyl halide such as methyl iodide in diethyleneglycol dimethyl ether to yield compounds of the general formula

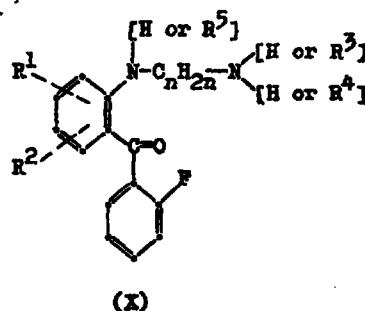


wherein A, B, R¹, R², R³, R⁴, R⁵, n and the broken lines have the significance given earlier, which, upon hydrolysis by heating under reflux in hydrochloric acid, yield compounds of formula I hereinbefore in which R³ or R⁴ is present. The N,N - di(lower alkyl) compounds can be manufactured by lower-alkylation of the corresponding amino or mono(lower alkyl)-amino compounds with a mixture of the appropriate aqueous aldehyde and formic acid. For example, compounds of formula I in which R³ and R⁴ both represent a methyl group can be manufactured from the corresponding compounds in which R³ and R⁴ are both absent by methylation with a mixture of aqueous formaldehyde and formic acid.

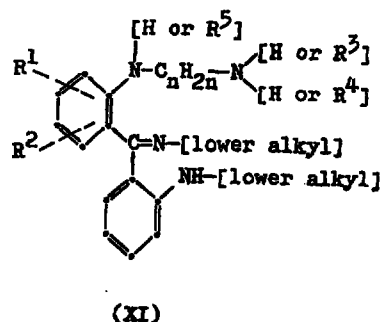
Compounds of formula I hereinbefore in which A represents an =N—OH group (oximes) can be manufactured from the corresponding compounds of formula I in which A represents an oxygen atom (ketones) by reaction with hydroxyl amine. This reaction is preferably carried out in the presence of a suitable inert organic solvent such as pyridine or ethanol.

Compounds of formula I hereinbefore in which A represents an =NH or an =N—(lower alkyl) group can be manufactured from the corresponding compounds of formula I in which A represents an oxygen atom (ketones) by reaction with ammonia or a lower-alkyl amine under pressure. The reaction with ammonia results in compounds of formula I in which A represents an =NH group and the reaction with a lower-alkyl amine results in compounds in which A represents an =N—(lower alkyl) group.

Compounds of formula I hereinbefore in which B represents a fluoro-phenyl group can be converted into compounds of formula I in which B represents a (lower alkylamino)-phenyl group, the C=O group (if present) being simultaneously replaced by the C=N—(lower alkyl) group. Thus, for example, when a compound of the general formula

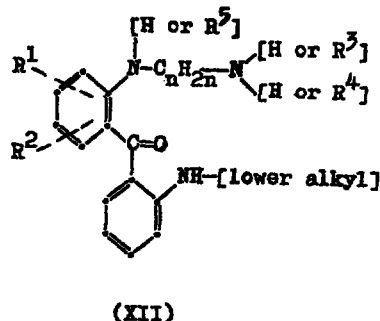


wherein R¹, R², R³, R⁴, R⁵, n and the broken lines have the significance given earlier, is reacted with at least 2 mols of a lower-alkyl amine under pressure there are obtained compounds of the general formula



wherein R¹, R², R³, R⁴, R⁵, n and the broken lines have the significance given earlier.

Further, any imine product obtained can be hydrolysed with a strong acid to give a ketone. Thus, for example, a compound of formula XI can be hydrolysed with a strong acid to yield a compound of the general formula

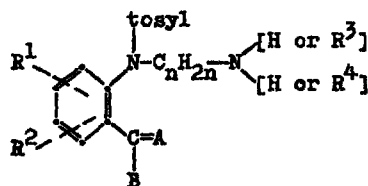


wherein R¹, R², R³, R⁴, R⁵, n and the broken lines have the significance given earlier, which, in turn, can be converted into the corresponding oxime or imine by reaction with hydroxyl amine or ammonia under pressure as described earlier.

The compounds of formula I form acid

addition salts with one or more molar equivalents of acid depending upon the number of basic nitrogen atoms present. For example, they form acid addition salts with inorganic and organic acids such as hydrochloric acid, hydrobromic acid, citric acid, phosphoric acid, tartaric acid, salicylic acid, toluenesulphonic acid, ascorbic acid, nitric acid, succinic acid and formic acid.

The products obtained by reacting a compound of formula IV hereinbefore in which X represents a tosyl-amino group with a compound of formula V hereinbefore in which Y represents a halogen atom have the general formula



(XIII)

(wherein A, B, R^1 , R^2 , R^3 , R^4 , n and the broken lines have the significance given earlier). The products of formula XIII in which A represents an oxygen atom, B represents a phenyl, halo-phenyl or trifluoromethyl-phenyl group, R is absent, R^3 (when present) represents a halogen atom or the trifluoromethyl group, R^3 and R^4 each represent a lower-alkyl group, n stands for 2, 3, 4, 5, 6 or 7 (at least one of R^3 and R^4 being present when n stands for 2) are claimed *per se* in the specification of our copending Application for Letters Patent No. 18,508/68 (now Serial No. 1148623).

The following Examples illustrate the processes provided by the invention:

EXAMPLE 1

900 ml of ethanol and 900 ml of 3-N hydrochloric acid were added to 161 g (0.360 mol) of 7-chloro-1-(3-dimethylamino-propyl)-5-fluoro-phenyl-2,3-dihydro-1H-benzodiaz[1,4]epinone-(2) dihydrochloride. The resulting solution was heated under reflux for 8 hours, then most of the ethanol was removed under reduced pressure. The residual solution was made basic ($>pH9$, HYDRON papers) with concentrated ammonium hydroxide, the solution being kept at approximately room temperature by the addition of ice. The resulting mixture was extracted with two 300 ml portions of methylene chloride and the combined organic extracts were washed with 200 ml of brine and dried over anhydrous sodium sulphate. 100

ml of benzene were added to the dried extracts and the mixture was evaporated to dryness. A solution of 127 g of the oil thus obtained in 200 ml of petroleum ether was filtered (without suction) through a column containing 400 g of Grade I neutral alumina. Elution of the column with 1300 ml of petroleum ether gave a first fraction which upon evaporation yielded 5-chloro-2-[N-(3-dimethylamino-propyl)-amino]-2'-fluoro-benzophenone in the form of an oil. The oil thus obtained was dissolved in 160 ml of methanol and 40 ml of 8.46-N methanolic hydrogen chloride (10% excess) were added. 800 ml of ether were slowly added to the mixture and the resulting solution was cooled overnight. Filtration, washing of the filter-cake with ether and drying overnight at $55^\circ C$ then gave 5-chloro-2-[N-(3-dimethylamino-propyl)-amino]-2'-fluoro-benzophenone hydrochloride in the form of yellow rods having a melting point of $172^\circ-174^\circ C$.

5-chloro-2-[N-(3-dimethylamino-propyl)-amino]-2'-fluoro-benzophenone was further treated as follows:

i) A solution of 16.7 g (49.8 mmol) of 5-chloro-2-[N-(3-dimethylamino-propyl)-amino]-2'-fluoro-benzophenone, 85 g of hydroxyl amine hydrochloride and 200 ml of pyridine was heated at reflux for 24 hours. A further 15 g of hydroxyl amine hydrochloride were then added and the heating at reflux was continued for a total of 96 hours. The reaction mixture was then poured into an excess of iced 3-N sodium hydroxide. The thus cooled mixture was extracted with methylene chloride and washed with water and the solvent was removed to give a solid. Crystallization of the solid from ether and subsequent recrystallization from ethanol gave colourless needles of 2-[N-(3-dimethylamino-propyl)-amino]-5-chloro-2'-fluoro-benzophenone oxime melting at $170^\circ-171^\circ C$.

ii) A mixture of 34.5 g (0.103 mol) of 5-chloro-2-[N-(3-dimethylamino-propyl)-amino]-2'-fluoro-benzophenone, 1.0 g of zinc chloride and an excess of methyl amine in 250 ml of ethanol was sealed in a bomb under nitrogen at a pressure of 1000 pounds per square inch and shaken at $150^\circ C$ for *ca* 3 hours. The resulting mixture was filtered and the filtrate was concentrated *in vacuo* to give a mixture of two isomeric 5-chloro-2-[N-(3-dimethylamino-propyl)-amino]-2'-methylamino-benzophenone N-methyl-imines in the form of yellow prisms of melting point $90^\circ-103^\circ C$ (if desired, the isomers could be separated: fractional recrystallization from hexane gave isomer "a" melting at $109^\circ-111^\circ C$ and concentration of the mother liquors gave isomer "b" melting at $110^\circ-113^\circ C$).

5.0 g of 5-chloro-2-[N-(3-dimethyl-

- amino - propyl) - amino] - 2' - methyl-
amino - benzophenone N - methyl - imine
were dissolved in 50 ml of ethanol and 100
ml of 3 - N hydrochloric acid. The solution
5 was heated at reflux for 3.5 hours, then
neutralised and extracted with methylene
chloride. The methylene chloride extract was
dried and the solvent removed *in vacuo* to
give an orange oil. Crystallization from hex-
ane/petrol gave 5 - chloro - 2 - [N - (3 -
10 dimethylamino - propyl) - amino] - 2' -
methylamino - benzophenone in the form of
yellow prisms of melting point 85°—87°C.

EXAMPLE 2

- 15 A) The preparation of the starting material:
A solution of 10 g (31.7 mmol) of 7 -
bromo - 5 - [pyridyl - (4)] - 2,4 - dihydro -
1H - benzdiaz[1,4]epinone - (2) in 150 ml of
freshly distilled N,N - dimethyl - formamide
20 was stirred for 4 hours at room temperature
under dry nitrogen with 1.95 g (50 mmol)
of sodamine. An excess of a dried chloro-
form solution of 1 - chloro - 3 - dimethyl-
amino - propane was then added and the
25 resulting mixture was stirred overnight. The
mixture was then diluted with 300 ml of
water and extracted with chloroform. The
chloroform extract was washed three times
with water, dried over magnesium sulphate
30 and concentrated *in vacuo* to give a dark oil.
The oil was washed five times with 100 ml
portions of hexane, then the insoluble solid
was extracted continuously with hexane over a
period of 20 hours. The hexane solutions
35 were combined and concentrated to a volume
of ca 250 ml. The precipitate which formed
on standing overnight was separated by filtra-
tion. Removal of the hexane gave an oil, crys-
tallization of which from ether/hexane gave
40 colourless prisms of melting point 92°—98°C.
Two recrystallizations from ether/cyclohexane
gave colourless prisms of 7 - bromo - 1 -
(3 - dimethylamino - propyl) - 5 - [pyridyl -
(4)] - 2,3 - dihydro - 1H - benzdiaz[1,4] -
45 epinone - (2) of melting point 97.5°—99°C.

B) The process:

- A solution of 1.0 g (2.5 mmol) of 7 -
bromo - 1 - (3 - dimethylamino - propyl) -
5 - [pyridyl - (4)] - 2,3 - dihydro - 1H -
50 benzdiaz[1,4]epinone - (2) in 35 ml of a 1:1
mixture of 6-N hydrochloric acid and ethanol
was heated at reflux for 7 hours. The result-
ing mixture was made basic with 3-N sodium
hydroxide and extracted four times with ether.
55 The combined ether extracts were dried over
magnesium sulphate and concentrated *in vacuo*
to give 4 - [5 - bromo - 2 - [N - (3 -
(3 - dimethylamino - propyl) - amino] -
benzoyl] - pyridine. An ethanolic solution of
60 this base was treated with maleic acid and the
resulting salt recrystallized from ethanol/ether
to give 4 - [5 - bromo - 2 - [N - (3 - di-
methylamino - propyl) - amino] - benzoyl] -

pyridine maleate in the form of yellow prisms
of melting point 148°—151°C. Recrystalliza- 65
tions from ethanol/ether raised the melting
point of the salt to 151°—152°C.

EXAMPLE 3

A solution of 36.9 g (0.1 mol) of 7 -
chloro - 1 - (2 - diethylamino - ethyl) - 5 - 70
phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]-
epinone - (2) in 200 ml of ethanol and 200
ml or 3-N hydrochloric acid was stirred at
reflux for 8 hours. The ethanol was then re-
moved *in vacuo* and the residue poured into 75
an excess of iced ammonium hydroxide. The
basic mixture was extracted with methylene
chloride and the methylene chloride extract
was dried over magnesium sulphate and con-
centrated *in vacuo* to give 2 - [N - (2 -
80 diethylamino - ethyl) - amino] - 5 - chloro -
benzophenone. An ethereal solution of this
base was treated with hydrogen chloride to
give, after recrystallization from isopropanol,
2 - [N - (2 - diethylamino - ethyl) - amino] - 85
5 - chloro - benzophenone hydrochloride
hemihydrate in the form of yellow prisms of
melting point 197°—199°C.

EXAMPLE 4

A solution of 17 g of 7 - chloro - 1 - 90
(2 - diethylamino - ethyl) - 5 - (2 - fluoro -
phenyl) - 2,3 - dihydro - 1H - benzdiaz-
[1,4]epinone - (2) dihydrochloride in a mix-
ture of 200 ml of ethanol and 200 ml of 95
3-N hydrochloric acid was heated under re-
flux for 18 hours. Ethanol was then removed
under reduced pressure and the residue was
made basic with ammonium hydroxide and
extracted with two 100 ml portions of ether.
100 The combined ether extracts were washed
with water, dried and evaporated to leave a
yellow oil. This oil was dissolved in hexane
and chromatographed over activated neutral
alumina. The petroleum ether (boiling point
105 =30—60°C) fraction from the column which
contained 5 - chloro - 2 - [N - (2 - diethyl-
amine - ethyl) - amino] - 2' - fluoro - benzo-
phenone was concentrated and the concentrate
was dissolved in ether. The ethereal solution
was saturated with dry hydrogen chloride, 110
when 5 - chloro - 2 - [N - (2 - diethyl-
amino - ethyl) - amino] - 2' - fluoro - benzo-
phenone hydrochloride precipitated as a
yellow crystalline salt of melting point 134°—
115 143°C and was separated by filtration.

EXAMPLE 5

A solution of 17 g of 7 - chloro - 1 -
(3 - diethylamino - propyl) - 5 - (2 -
fluoro - phenyl) - 2,3 - dihydro - 1H - 120
benzdiaz[1,4]epinone - (2) dihydrochloride in
a mixture of 200 ml of ethanol and 200 ml
of 3-N hydrochloric acid was heated under
reflux for 18 hours. Ethanol was then re-
moved under reduced pressure and the resi- 125
due was made basic with ammonium hydrox-

ide and extracted with two 100 ml portions of ether. The combined ether extracts were washed with water, dried and evaporated to leave an oil. This oil was dissolved in hexane and the hexane solution was put on a column of activated neutral alumina and chromatographed with petroleum ether (boiling point = 30°—60°C). The petroleum ether fraction which contained 5 - chloro - 2 - [N - (3 - diethylamino - propyl) - amino] - 2' - fluoro - benzophenone was concentrated. The concentrate was added to an ether/acetone mixture which was then saturated with dry hydrogen chloride to yield 5 - chloro - 2 - [N - ((3 - diethylamino - propyl) - amino) - 2' - fluoro - benzophenone hydrochloride in the form of bright yellow prisms of melting point 114°—117°C.

EXAMPLE 6

20 A solution of 17 g of 7 - bromo - (3 - dimethylamino - propyl) - 5 - [pyridyl - (2)] - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) dihydrochloride in a mixture of 200 ml of ethanol and 200 ml of 3-N hydrochloric acid was heated under reflux for 18 hours. Ethanol was then removed under reduced pressure and the residue was made basic with ammonium hydroxide and extracted with two 100 ml portions of ether. The combined ether extracts were washed with water, dried and evaporated to leave an oil. Chromatography of this crude product over neutral activated alumina gave, upon evaporation of the ethyl acetate fraction from the column, 2 - [5 - bromo - 2 - [N - (3 - dimethylamino - propyl) - amino] - benzoyl] - pyridine as a yellow oil. This was dissolved in a small amount of ethanol and dry hydrogen chloride was bubbled into the solution. The addition of ether caused 2 - [5 - bromo - 2 - [N - (3 - dimethylamino - propyl) - amino] - benzoyl] - pyridine dihydrochloride hemihydrate to precipitate as orange rods of melting point 177°—185°C (with decomposition). Although dry hydrogen chloride was employed, the hemihydrate product was obtained owing to sufficient water being present in the ethanol and/or in the atmosphere.

EXAMPLE 7

50 17 g of 7 - chloro - 1 - (3 - dimethylamino - propyl) - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) in a mixture of 200 ml of ethanol and 200 ml of 3-N hydrochloric acid were heated under reflux for 18 hours. Ethanol was then removed under reduced pressure and the residue was made basic with ammonium hydroxide and extracted with two 100 ml portions of ether. The combined ether extracts were washed with water, dried and evaporated to leave an oil. This oil was dissolved in hexane and chromatographed over active neutral alumina. Evaporation of the ethyl acetate fraction from

the column yielded 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - amino] - benzophenone as an oil. The free base thus obtained was dissolved in isopropanol. Dry hydrogen chloride was passed into the solution, then ether was added and 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - amino] - benzophenone hydrochloride precipitated. Recrystallization from a methanol/ether mixture gave the salt as yellow prisms of a melting point 157°—163°C.

EXAMPLE 8

A solution of 5.5 g of 7 - chloro - 5 - (2 - fluoro - phenyl) - 1 - [3 - (1 - piperazinyl) - propyl] - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) in a mixture of 50 ml of ethanol and 50 ml of 3-N hydrochloric acid was heated at reflux for 5 hours. The ethanol was then removed under reduced pressure and the residue was made alkaline with ammonium hydroxide. The resulting oil was extracted with methylene chloride and the extract was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated to a small volume. The concentrate was put on a column of WOELM Grade I neutral alumina and chromatographed with ethyl acetate to give a viscous yellow oil. This oil was treated with a methanolic solution of maleic acid and allowed to stand overnight. Filtration then yielded bright yellow crystals of 5 - chloro - 2 - [N - [3 - (1 - piperazinyl) - propyl] - amino] - 2' - fluoro - benzophenone dimaleate melting at 157°—159°C.

EXAMPLE 9

A solution of 6 g of 7 - chloro - 5 - (2 - fluoro - phenyl) - 1 - [3 - (4 - methyl - 1 - piperazinyl) - propyl] - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) in a mixture of 50 ml of ethanol and 50 ml of 3-N hydrochloric acid was heated at reflux for 4 hours. Ethanol was then removed under reduced pressure and the residue was made alkaline with ammonium hydroxide and extracted with methylene chloride. The extract was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated to a small volume. The concentrate was chromatographed over WOELM neutral alumina with ethyl acetate to give a yellow oil. This oil was dissolved in methanol and treated with a methanolic solution of maleic acid. Filtration gave a yellow solid which was recrystallized from ethanol to yield brilliant yellow prisms of 5 - chloro - 2 - [N - [3 - (4 - methyl - 1 - piperazinyl) - propyl] - amino] - 2' - fluoro - benzophenone dimaleate at 185°—188°C.

EXAMPLE 10

A solution of 3.5 g of 7 - chloro - 5 - (2 - fluoro - phenyl) - 1 - [3 - [4 - (2 -

hydroxy - ethyl) - 1 - piperazinyl] - 1 - piperazinyl] - propyl] - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) in a mixture of 50 ml of ethanol and 50 ml of 3-N hydrochloric acid was heated at reflux for 6 hours. Ethanol was then removed under reduced pressure and the residue was made alkaline with ammonium hydroxide and extracted with methylene chloride. The methylene chloride extract was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated to a small volume. The concentrate was put on a column of neutral alumina and chromatographed with ethyl acetate to give 5 - chloro - 2 - [N - [3 - [4 - (2 - hydroxy - ethyl) - 1 - piperazinyl] - propyl] - amino] - 2' - fluoro - benzophenone as a yellow oil. This yellow oil was treated with a methanolic solution of 2 g of maleic acid. Filtration gave a yellow solid which was recrystallized from acetone to give small yellow needles of 5 - chloro - 2 - [N - [3 - [4 - (2 - hydroxy - ethyl) - 1 - piperazinyl] - propyl] - amino] - 2' - fluoro - benzophenone dimaleate melting at 166°—167°C.

EXAMPLE 11

A solution of 6 g of 7 - chloro - 5 - (2 - fluoro - phenyl) - 1 - [3 - [4 - (2 - vinyloxy - ethyl) - 1 - piperazinyl] - propyl] - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) in a mixture of 85 ml of 3-N hydrochloric acid and 75 ml of ethanol was heated at reflux for 9 hours. The ethanol was then removed under reduced pressure and the residue was made alkaline with ammonium hydroxide and extracted with methylene chloride. The methylene chloride extract was washed with three 150 ml portions of brine, dried over anhydrous sodium sulphate, filtered and concentrated to a small volume. The concentrate was put on a column of neutral alumina and chromatographed with a 50:50 (v/v) mixture of ethyl ether and ethyl acetate to yield 5 - chloro - 2 - [N - [3 - [4 - (2 - vinyloxy - ethyl) - 1 - piperazinyl] - propyl] - amino] - 2' - fluoro - benzophenone as a yellow oil. This yellow oil was treated with a methanolic solution of maleic acid and the resulting solution was allowed to stand overnight. The solid was then filtered off and recrystallized from acetone to give 5 - chloro - 2 - [N - [3 - [4 - (2 - vinyloxy - ethyl) - 1 - piperazinyl] - propyl] - amino] - 2' - fluoro - benzophenone dimaleate as bright yellow prisms of melting point 140°—142°C.

EXAMPLE 12.

A solution of 4.8 g of 7 - chloro - 1 - [3 - [4 - (ethoxy - ethyl) - 1 - piperazinyl] - propyl] - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) trimaleate in 85 ml of 3-N hydrochloric acid and 80 ml of ethanol was heated at reflux for 10 hours. The ethanol was then removed

under reduced pressure and the residue was made alkaline with ammonium hydroxide and extracted with methylene chloride. The methylene chloride extract was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated to a small volume. The concentrate was put on a column of neutral alumina and chromatographed with ethyl acetate to give 5 - chloro - 2 - [N - [3 - [4 - (2 - ethoxy - ethyl) - 1 - piperazinyl] - propyl] - amino] - 2' - fluoro - benzophenone as a yellow oil. This yellow oil was treated with a solution of maleic acid in methanol and the solution obtained was allowed to stand overnight. The resulting yellow solid was recrystallized from acetone to yield yellow prisms of 5 - chloro - 2 - [N - [3 - [4 - (2 - ethoxy - ethyl) - piperazinyl] - propyl] - amino] - 2' - fluoro - benzophenone dimaleate melting at 153°—155°C.

EXAMPLE 13

A) The preparation of the starting material:

A mixture of 7.3 g (0.02 mol) of 7 - chloro - 1 - (3 - chloro - propyl) - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2), 3.0 g (0.02 mol) of sodium iodide, 7 g (0.08 mol) of morpholine and 75 ml of methyl ethyl ketone was heated at reflux for 22 hours. Solvents were then removed under reduced pressure and the residue was partitioned between water and methylene chloride. The methylene chloride extract was washed with brine and extracted with 3-N hydrochloric acid. The combined acid extracts were made basic with ammonium hydroxide and re-extracted with methylene chloride. The last-mentioned methylene chloride extracts were washed with brine, dried over sodium sulphate and concentrated to give a yellow oil. This was treated with a solution of maleic acid in methanol. The white solid which formed was recrystallized from methanol to yield colourless platelets of 7 - chloro - 5 - (2 - fluoro - phenyl) - 1 - (3 - morpholino - propyl) - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) monomaleate melting at 183°—185°C.

B) The process:

A solution of 5.9 g of 7 - chloro - 5 - (2 - fluoro - phenyl) - 1 - (3 - morpholino - propyl) - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2) in a mixture of 70 ml of 3-N hydrochloric acid and 70 ml of ethanol was heated at reflux for 9 hours. The ethanol was then removed under reduced pressure and the residue was made alkaline with ammonium hydroxide and extracted with methylene chloride. The methylene chloride extract was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated to a small volume. The concentrate was put on a column of neutral alumina and chromato-

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graphed with ethyl ether. Concentration of the ethyl ether gave 5 - chloro - 2 - [N - (3 - morpholino - propyl) - amino] - 2' - fluoro - benzophenone as an oil. This oil was dissolved in methanol and the resulting solution was saturated with hydrogen chloride. The yellow solid which formed was recrystallized from methanol/ether to yield 5 - chloro - 2 - [N - (3 - morpholino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride in the form of yellow needles of melting point 148°—150°C.

EXAMPLE 14

A solution of 1.3 g of 1 - (2 - dimethylamino - ethyl) - 5 - phenyl - 7 - trifluoromethyl - 2,3 - dihydro - 1H - benzodiaz[1,4]epinone - (2) dihydrochloride in 50 ml of ethanol and 40 ml of 3-N hydrochloric acid was heated at reflux for 8 hours. The ethanol was then removed under reduced pressure and the residue was made alkaline with ammonium hydroxide and extracted with methylene chloride. The methylene chloride extract was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated to a small volume. The concentrate was put on a column of neutral alumina and chromatographed with ethyl acetate. Concentration of the ethyl acetate gave 2 - [N - (2 - dimethylamino - ethyl) - amino] - 5 - trifluoromethyl - benzophenone as an oil. This oil was dissolved in ethanol and the solution was saturated with hydrogen chloride. Treatment with ether gave a yellow solid which was recrystallized from ethanol/ether to yield 5 - trifluoromethyl - 2 - [N - (2 - dimethylamino - ethyl) - amino] - benzophenone hydrochloride in the form of yellow needles of melting point 203°—205°C.

EXAMPLE 15

A solution of 3.6 g of 1 - (3 - dimethylamino - propyl) - 7 - nitro - 5 - phenyl - 2,3 - dihydro - 1H - benzodiaz[1,4]epinone - (2) hydrochloride in 50 ml of a 50:50 mixture of ethanol and 3-N hydrochloric acid was heated on the steam-bath for 7 hours. The resulting mixture was diluted with ice-water, made alkaline with dilute sodium hydroxide and extracted with methylene chloride. The organic layer was dried and concentrated to dryness *in vacuo*. The residue was crystallized and recrystallized from ether to yield 2 - [N - (3 - dimethylamino - propyl) - amino] - 5 - nitro - benzophenone as yellow prisms of melting point 105°—106°C. 2 - [N - (3 - dimethylamino - propyl) - amino] - 5 - nitro - benzophenone was dissolved in an excess of methanolic hydrogen chloride. The solution was concentrated to dryness *in vacuo* and the residue was crystallized from a mixture of methanol, isopropanol and ether. After recrystallization from the same solvent mixture, 2 - [N - (3 -

dimethylamino - propyl) - amino] - 5 - nitro - benzophenone hydrochloride was obtained as yellow needles of melting point 181°—182°C.

EXAMPLE 16

A mixture of 50 g of 7 - bromo - 1 - (3 - dimethylamino - propyl) - 5 - phenyl - 2,3 - dihydro - 1H - benzodiaz[1,4]epinone - (2) and 200 ml of 3-N hydrochloric acid was heated on a steam bath for 4 hours. The resulting mixture was left at room temperature for 18 hours, then diluted with water and extracted with ether. The aqueous acidic layer was separated, made alkaline with dilute sodium hydroxide and extracted with ether. The ether layer containing 5 - bromo - 2 - [N - (3 - dimethylamino - propyl) - amino] - benzophenone was separated, dried and concentrated to dryness *in vacuo*. The residue was dissolved in 100 ml of an ethanolic solution of maleic acid (excess), heat being applied until complete solution was obtained. The solution was concentrated to dryness *in vacuo* and the residue was crystallized and recrystallized from a mixture of methylene chloride and ether to yield 5 - bromo - 2 - [N - (3 - dimethylamino - propyl) - amino] - benzophenone maleate in the form of yellow needles of melting point 110°—111°C.

In a manner analogous to that described in the preceding Examples, but in each case using the appropriate starting materials, the following diamines can be obtained:

2 - [N - (3 - amino - propyl) - amino] - 5 - nitro - benzophenone (yellow needles of melting point 97°—98°C after recrystallization from ether); 2 - [N - (3 - amino - propyl) - amino] - 5 - nitro - benzophenone hydrochloride (yellow needles of melting point 239°—240°C after recrystallization from a mixture of methanol and ether); 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - benzophenone (yellow rods of melting point 64°—66°C after recrystallization from petroleum ether); 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone monohydrochloride (yellow crystals of melting point 205°—215°C); 5 - chloro - 2 - [N - (2 - methylamino - ethyl) - N - methyl - amino] - benzophenone monohydrobromide (yellow prisms of melting point 145°—150°C after recrystallization from acetone and additional recrystallization from isopropanol/ether); 5 - chloro - 2 - [N - (3 - amino - propyl) - amino] - benzophenone hydrochloride (yellow needles of melting point 170°C after recrystallization from isopropanol/ether); 5 - chloro - 2 - [N - (3 - methylamino - propyl) - amino] - benzophenone hydrochloride (melting point 200°—205°C) and 5 - chloro - 2 - [N - (3 - piperidino - propyl) - amino] - benzophenone hydrochloride (yellow plates of melting point

208°—210°C after recrystallization from ethanol).

EXAMPLE 17

- A) The preparation of the starting material:
- 5 A solution of 23.2 g (86 mmol) of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benz[diaz[1,4]epin in 250 ml of benzene and 100 mmol of dimethyl sulphate was heated at reflux overnight. The solvent was then removed *in vacuo* and the residue recrystallized from (methylene chloride)/ether to give 7 - chloro - 1,4 - dimethyl - 5 - phenyl - 2,3 - dihydro - 1H - benz[diaz[1,4]epinium methosulphate as orange prisms
- 10 of melting point 118°—126°C.

B) The process:

- A solution of 30.6 g (78 mmol) of 7 - chloro - 1,4 - dimethyl - 5 - phenyl - 2,3 - dihydro - 1H - benz[diaz[1,4]epinium methosulphate in 50 ml of water was stirred at 0°C. An equimolar amount (78 mmol) of sodium hydroxide in 50 ml of water chilled to 0°C was added dropwise to the aqueous medium over a period of 0.5 hour. When the addition was about half completed, 50 ml of ether was added to dissolve the free base formed. The mixture obtained after complete addition was extracted with ether, dried over magnesium sulphate and concentrated *in vacuo* to give 5 - chloro - 2 - [N - (2 - methylamino - ethyl) - N - methyl - amino] - benzophenone. The base was dissolved in ether and ethereal solution was treated with hydrogen bromide to yield 5 - chloro - 2 - [N - (2 - methylamino - ethyl) - N - methyl - amino] - benzophenone dihydrobromide of melting point 150°—160°C. Recrystallization from acetone gave yellow prisms of unchanged melting point. Additional recrystallizations from isopropanol/ether gave the monohydrobromide as yellow prisms of melting point 145—150°C.

EXAMPLE 18

- A) The preparation of the starting material:
- 45 A mixture of 13.0 g of 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benz[diaz[4]epine and 100 ml of ethyl iodide was heated at reflux on a steam-bath for 1 hour, then evaporated to dryness *in vacuo*. The residue was dissolved in a small amount of methanol and the resulting solution added to 1.5 litres of water. The pH of the resulting medium was adjusted to 7—8 with ammonium hydroxide. Tars were removed by filtration through cotton and the aqueous filtrate was washed with ether and evaporated to dryness *in vacuo*. Isopropanol was added to the residue and 7 - chloro - 4 - ethyl - 5 - phenyl - 2,3 - dihydro - 1H - benz[diaz[1,4]epinium iodide separated as yellow crystals melting at 208°—212°C. Recrystallization from a methanol/ether mixture gave yellow prisms melting at 210°—212°C.

B) The process:

- 2.8 g (6.8 mmol) of 7 - chloro - 4 - ethyl - 5 - phenyl - 2,3 - dihydro - 1H - benz[diaz[1,4]epinium iodide in a mixture of 300 ml of water and 50 ml of ethanol were stirred at room temperature. An equimolar amount of 1-N sodium hydroxide solution was carefully added to the stirred mixture, which was then diluted with an additional 100 ml of water and extracted with ether. The ether extract was washed three times with water and once with brine, dried over sodium sulphate and concentrated *in vacuo* to a yellow oil. The oil was crystallized from petroleum ether. Upon recrystallization from petroleum ether, 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - benzophenone was obtained as yellow rods of melting point 64°—66°C.

EXAMPLE 19

- A) The preparation of the starting material:
- A mixture of 32.0 g of 7 - chloro - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - benz[diaz[1,4]epine and 260 ml of ethyl iodide was heated at reflux on a steam-bath for 2 hours. The excess ethyl iodide was then removed *in vacuo* and the residue was dissolved in warm isopropanol. Ether was added and 7 - chloro - 4 - ethyl - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - benz[diaz[1,4]epinium iodide melting at 240°—245°C appeared as a red crystalline precipitate. Recrystallization from (methylene chloride)/isopropanol/ether gave the quaternary iodide as orange rods melting at 244°—247°C.

B) The process

- A solution of 15.0 g (34.8 mmol) of 7 - chloro - 4 - ethyl - 5 - (2 - fluoro - phenyl) - 2,3 - dihydro - 1H - benz[diaz[1,4]epinium iodide in 300 ml of methanol was stirred at room temperature. An equimolar amount of 1-N sodium hydroxide was carefully added to the stirred medium. The methanol was then removed *in vacuo* and 200 ml of water were added to dissolve the residual yellow oil. The aqueous solution was extracted several times with ether and the combined ether extracts were washed twice with water and once with brine, dried over sodium sulphate and concentrated *in vacuo* to give 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone as a yellow oil. The oil was dissolved in a small amount of absolute ethanol. An excess of an ethanolic solution of hydrogen chloride was added to the solution and 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone monohydrochloride precipitated as yellow crystals of melting point 205°—215°C.

In a manner analogous to that described in Examples 17 to 19, but in each case using the appropriate starting materials, the following diamines can be obtained:

2 - [N - (2 - diethylamino - ethyl) - amino] - 5 - chloro - benzophenone hydrochloride hemihydrate (yellow prisms of melting point 197°—199°C after recrystallization from isopropanol); 5 - chloro - 2 - [N - (2 - diethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride (yellow crystalline salt of melting point 134°—143°C) and 5 - trifluoromethyl - 2 - [N - (2 - dimethylamino - ethyl) - amino] - benzophenone hydrochloric (yellow needles of melting point 203°—205°C after recrystallization from ethanol/ether).

EXAMPLE 20

104 g of 2 - chloro - 5 - nitro - benzophenone were added to a stirred mixture of 900 ml of pyridine and 200 ml of propylenediamine - (1,3). The resulting mixture was heated at reflux for 5 hours and then concentrated to dryness *in vacuo*. The residue was shaken with a mixture of methylene chloride and water and the organic layer was separated, dried and concentrated to dryness *in vacuo*. The residue was dissolved in 1 litre of 1.5 - N hydrochloric acid and the solution was stirred and heated at reflux for 2 hours, then left at room temperature for 18 hours. The crystalline material which formed was separated by filtration and recrystallized from methanol. After recrystallization from a mixture of methanol and ether 2 - [N - (3 - amino - propyl) - amino] - 5 - nitro - benzophenone hydrochloride was obtained as yellow needles melting at 239°—240°C. Treatment of the hydrochloride with sodium hydroxide gave the free base, 2 - [N - (3 - amino - propyl) - amino] - 5 - nitro - benzophenone. Recrystallization of the base from ether yielded yellow needles of melting point 97°—98°C.

2 - [N - (3 - amino - propyl) - amino] - 5 - nitro - benzophenone was further treated as follows:

50 ml of 40% aqueous formaldehyde were added to a solution of 9.1 g of 2 - [N - (3 - amino - propyl) - amino] - 5 - nitro - benzophenone in 50 ml of formic acid. The resulting mixture was heated on a steam-bath for 1.5 hours, then heated at reflux for 18 hours. The mixture was subsequently poured on to ice, made alkaline with dilute sodium hydroxide solution and extracted with ether. The ether extract was dried and concentrated to dryness *in vacuo* and the residue was dissolved in ether and extracted with dilute hydrochloric acid. The aqueous acidic layer was separated, made alkaline with dilute sodium hydroxide solution and extracted with ether. The last-mentioned ether extract was dried and concentrated to dryness *in vacuo*. The residue was dissolved in an excess of methanolic hydrogen chloride and the solution concentrated to dryness *in vacuo*. The residue was crystallized from a mixture of

methanol, isopropanol and ether to yield 2 - [N - (3 - dimethylamino - propyl) - amino] - 5 - nitro - benzophenone hydrochloride melting at 180°—181°C.

EXAMPLE 21

i)a A solution of 0.013 mol of 5 - chloro - 2 - *paratoluenesulphonamido* - benzophenone in 25 ml of N,N - dimethyl - formamide was treated with 3.2 ml of a solution (containing 4.87 meq/ml) of sodium methoxide in methanol (0.156 mol). The resulting mixture was stirred at room temperature for 0.5 hour, after which time a solution of 0.325 mol of 3 - dimethylamino - propyl chloride in 25 ml of toluene was added. The mixture was then stirred at 55°C for 18 hours and concentrated to an oil which was dissolved in 200 ml of ether. The solution was washed with three 100 ml portions of water and extracted with three 50 ml portions of 6-N hydrochloric acid. The combined acid extracts were washed with 100 ml of ether, made basic with ammonia and extracted with three 100 ml portions of ether. The ether extracts were combined, washed with water, dried over anhydrous sodium sulphate and concentrated, whereupon 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - *paratoluenesulphonamido*] - benzophenone crystallized. Recrystallization from a mixture of ether and petroleum ether gave white prisms of melting point 103°—106°C.

i)b A solution of 15 g (0.0421 mol) of the sodio derivative of 2 - (*paratoluenesulphonamido*) - 5 - chloro - benzophenone in 50 ml of N,N - dimethyl - formamide was treated with 5 ml (0.0505 mol) of 1 - bromo - 3 - chloro - propane and the mixture was stirred at 60°—70°C for 18 hours. The solvent was subsequently removed under reduced pressure and the residual oil was dissolved in 100 ml of methylene chloride. The solution was washed with two 100 ml portions of water and 75 ml of saturated brine and dried over anhydrous sodium sulphate. The dried solution was evaporated and the resulting oil was dissolved in 50 ml of benzene and chromatographed over a column of 400 g of alumina. Elution with 1 litre of a 5% ether in benzene mixture gave 0.8 g of an oil which was mainly starting material and was discarded. Using ethyl acetate as the eluant (1 litre), a mixture of the two possible products was obtained. After removal of the solvent, the residue was crystallized from a mixture of methanol and petroleum ether (30°—60°C) to give the less soluble 5 - chloro - 2 - [N - (3 - bromo - propyl) - *paratoluenesulphonamido*] - benzophenone as white prisms melting at 104°C.

The crystalline material was added to the mother liquors containing 5 - chloro - 2 - [N - (3 - chloro - propyl) - *paratoluenesulphonamido*] - benzophenone and solvents were removed. A solution of 10 g of the resi-

dual mixture in 60 ml of N,N - dimethyl - formamide was treated with 5 g of sodium iodide and 60 ml of dimethyl amine. The resulting mixture was stirred at room temperature for 24 hours using a dry-ice condenser to prevent the escape of dimethyl amine. Solvent was then removed under reduced pressure and the resulting oil was triturated with 150 ml of ether and 150 ml of 3-N hydrochloric acid. The solution was decanted from any insoluble oil and the acid layer was separated, washed with 150 ml of ether and made basic with ammonium hydroxide. The basic medium was extracted with 150 ml of ether and the ether extract was washed with 100 ml of water and 100 ml of saturated brine, dried over anhydrous sodium sulphate, filtered and evaporated. The residue was crystallized from a mixture of ether and petroleum ether (30°—60°C) to give 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - paratoluenesulphonamido] - benzophenone as white prisms melting at 99°—104°C.

ii) 1.0 g of 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - paratoluenesulphonamido] - benzophenone was added to 20 ml of 70% (v/v) sulphuric acid maintained at a temperature of 105°C. The resulting solution was stirred, heated to 145°C and maintained at that temperature for 5 minutes. The solution was then poured over ice, made basic with concentrated ammonium hydroxide and extracted with three 50 ml portions of ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulphate and concentrated. An excess of a solution of dry hydrogen chloride in isopropanol was added to the concentrate to yield 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - amino] - benzophenone hydrochloride which was precipitated by the addition of ether and took the form of yellow prisms of melting point 157°—163°C.

EXAMPLE 22

A mixture of 9.0 g (29.2 mmol) of 2 - [N - (3 - chloro - propyl) - amino] - 5 - chloro - benzophenone, 30 mmol of potassium iodide and an excess of ammonia in 25 ml of ethanol was shaken at 100°C in a sealed container for 4 hours. The resulting mixture was filtered and the filtrate was concentrated to dryness *in vacuo*. The residue was partitioned between 3-N sodium hydroxide and methylene chloride. The methylene chloride layer was washed with water, dried over anhydrous sodium sulphate and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and chromatographed on a column of alumina (WOELM neutral, activity I). After passing benzene through the column, elution with 1% ethanol in benzene gave a fraction which upon evaporation yielded 2 - [N - (3 - amino - propyl) - amino] - 5 - chloro - benzophenone

as an oil. This oil was added to an excess of a solution of dry hydrogen chloride in ether to give 2 - [N - (3 - amino - propyl) - amino] - 5 - chloro - benzophenone hydrochloride which was recrystallized from isopropanol/ether to give yellow needles of melting point 170°C.

EXAMPLE 23

A mixture of 5.0 g (16 mmol) of 2 - [N - (3 - chloro - propyl) - amino] - 5 - chloro - benzophenone, 16 mmol of potassium iodide and an excess of methyl amine in ethanol was agitated in a sealed container at 100°—119°C for 4.5 hours. The resulting mixture was poured into 800 ml of water containing a small amount of sodium hydroxide and extracted with methylene chloride. The methylene chloride extract was washed with water and dried over anhydrous sodium sulphate and the solvent was removed to leave an oil. This oil was warmed in 3-N hydrochloric acid and the so-warmed medium was neutralised with sodium hydroxide. Extraction with methylene chloride and removal of the solvent gave a yellow oil which when treated with hydrogen chloride in ether gave 5 - chloro - 2 - [N - (3 - methylamino - propyl) - amino] - benzophenone hydrochloride of melting point 200°—205°C.

EXAMPLE 24

A mixture of 5.4 g (17.5 mmol) of 2 - [N - (3 - chloro - propyl) - amino] - 5 - chloro - benzophenone, 20 mmol of potassium iodide and 25 ml (excess) of piperidine was heated at reflux overnight. The resulting mixture was filtered and the piperidine removed from the filtrate *in vacuo*. The residue was dissolved in methylene chloride and the solution was washed with 1-N sodium hydroxide and then with water. The solvent was subsequently removed *in vacuo* to give 5 - chloro - 2 - [N - (3 - piperidino - propyl) - amino] - benzophenone as a yellow oil. 5 - Chloro - 2 - [N - (3 - piperidino - propyl) - amino] - benzophenone hydrochloride was obtained by adding the oil to methanolic hydrogen chloride. After recrystallization from ethanol, the salt was obtained as yellow plates of melting point 208°—210°C.

In a manner analogous to that described in Examples 20 to 24, but in each case using the appropriate starting materials, the following diamines can be obtained:

5 - Chloro - 2 - [N (3 - dimethylamino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride (yellow rods of melting point 172°—174°C). 5 - Chloro - 2 - [N - (2 - methylamino - ethyl) - N - methyl - amino] - benzophenone monohydrobromide (yellow prisms of melting point 145°—150°C after recrystallization from acetone and additional recrystallizations from isopropanol/ether); 4 - [5 - bromo - 2 - [N - (3 - dimethyl-

- amino - propyl) - amino] - benzoyl] - pyridine maleate (yellow prisms of melting point 151°—152°C after recrystallizations from ethanol/ether); 2 - [N - (2 - diethylamino - ethyl) - amino] - 5 - chloro - benzophenone hydrochloride hemihydrate (yellow prisms of melting point 197°—199°C after recrystallization from isopropanol); 5 - chloro - 2 - [N - (2 - diethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride (yellow crystalline salt of melting point 134°—143°C); 5 - chloro - 2 - [N - (3 - diethylamino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride (yellow prisms of melting point 144°—147°C); 2 - [5 - bromo - 2 - [N - (3 - dimethylamino - propyl) - amino] - benzoyl] - pyridine dihydrochloride hemihydrate [orange rods of melting point 177°—185°C (with decomposition)]; 5 - chloro - 2 - [N - (3 - diethylamino - propyl) - amino] - benzophenone hydrochloride (yellow prisms of melting point 157°—163°C after recrystallization from methanol/ether); 5 - chloro - 2 - [N - [3 - (1 - piperazinyl) - propyl] - amino] - 2' - fluoro - benzophenone dimaleate (yellow crystals of melting point 157°—159°C); 5 - chloro - 2 - [N - [3 - (4 - methyl - 1 - piperazinyl) - propyl] - amino] - 2' - fluoro - benzophenone dimaleate (yellow prisms of melting point 185°—188°C after recrystallization from ethanol); 5 - chloro - 2 - [N - [3 - [4 - (2 - hydroxy - ethyl) - 1 - piperazinyl] - propyl] - amino] - 2' - fluoro - benzophenone dimaleate (yellow needles of melting point 166°—167°C after recrystallization from acetone); 5 - chloro - 2 - [N - [3 - [4 - (2 - vinyloxy - ethyl) - piperazinyl] - propyl] - amino] - 2' - fluoro - benzophenone dimaleate (bright yellow prisms of melting point 140°—142°C after recrystallization from acetone); 5 - chloro - 2 - [N - [3 - [4 - (2 - ethoxy - ethyl) - piperazinyl] - propyl] - amino] - 2' - fluoro - benzophenone dimaleate (yellow prisms of melting point 153°—155°C after recrystallization from acetone); 5 - chloro - 2 - [N - (3 - morpholino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride (yellow needles of melting point 148°—150°C after recrystallization from methanol/ether); 5 - trifluoromethyl - 2 - [N - (2 - dimethylamino - ethyl) - amino] - benzophenone hydrochloride (yellow needles of melting point 203°—205°C after recrystallization from ethanol/ether); 2 - [N - (3 - dimethylamino - propyl) - amino] - 5 - nitro - benzophenone (yellow prisms of melting point 105°—106°C after recrystallization from ether); 5 - bromo - 2 - N[- (3 - dimethylamino - propyl) - amino] - benzophenone maleate (yellow needles of melting point 110°—111°C after recrystallization from (methylene chloride)/ether); 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - benzophenone (yellow rods of melting point 64°—66°C after recrystallization from petroleum ether) and 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone monohydrochloride (yellow crystals of melting point 205°—215°C).
- The following Examples illustrate the manufacture of pharmaceutical preparations containing the novel diamines provided by the invention:
- EXAMPLE A**
- Tablets each containing 25 mg of 5 - chloro - 2 - [N - (3 - diethylamino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride, 72 mg of lactose (spray dried), 2 mg of corn starch U.S.P. and 1 mg of calcium stearate and each having a total weight of 100 mg were manufactured by blending the active material, lactose, corn starch and calcium stearate in a suitable mixer, compressing the mixed powder on a heavy-duty tablet compressing machine to yield tablet slugs of ca 25 mm diameter and 6 mm thickness, passing the tablet slugs through a suitable comminuting machine to yield granules with a minimum of fines and recompressing the granulate on a tablet compressing machine using a 6 mm concave punch to an average tablet weight of 100 mg.
- EXAMPLE B**
- Capsules each containing 5 mg of 5 - chloro - 2 - [N - (3 - dimethylamino) - 2' - fluoro - benzophenone hydrochloride, 163 mg of lactose, 37 mg of corn starch and 5 mg of talc and each having a total net weight of 210 mg were manufactured by mixing the active material with the lactose and the corn starch in a suitable mixer, further blending the mixture by passing it through a comminuting machine with knives forward, returning the blended powder to the mixer, adding the talc, blending thoroughly and filling the resulting mixture into hard shell gelatin capsules on a capsulating machine.
- EXAMPLE C**
- Suppositories containing 0.010 g of 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride, 1.245 g of WECOBEE M (a refined synthetic cocoa butter, coconut derived) and 0.045 g of carnauba wax and each having a total weight of 1.3 g were manufactured by melting the WECOBEE M and the carnauba wax in a suitable size glass lined container, mixing the melt well, cooling it to 45°C, adding the active material (reduced to a fine powder with no lumps) to the cooled melt, stirring until the active material was completely and uniformly dispersed, pouring the mixture into suppository moulds to yield suppository dosage forms having an individual weight of 1.3 g, cooling the suppositories and removing them from the moulds; they were

then individually wrapped in wax paper for packaging.

EXAMPLE D

A dosage form of 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride suitable for parenteral use was manufactured by filling 50 mg of parenteral grade 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride (fibre-free) into a 5 ml ampoule utilizing an electric filler, sealing the ampoule and sterilizing it at 124°C for 2 hours; immediately before use, the powder is solubilized with 5 ml of water for injection.

EXAMPLE E

Tablets each containing 25 mg of 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride, 72 mg of lactose (spray dried), 2 mg of corn starch and 1 mg of calcium stearate and each having a total weight of 100 mg were manufactured by blending the active material, lactose, corn starch and calcium stearate in a suitable mixer, compressing the mixed powder on a heavy-duty tablet compressing machine to yield tablet slugs of ca 30 mm thickness, passing the tablet slugs through a suitable comminuting machine to yield granules with a minimum of fines and recompressing the granulate on a tablet compressing machine using a 6 mm standard concave punch to an average tablet weight of 100 mg.

EXAMPLE F

Capsules each containing 5 mg of 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride, 163 mg of lactose, 37 mg of corn starch and 5 mg of talc and each having a total net weight of 210 mg were manufactured by mixing the active material with the lactose and the corn starch in a suitable mixer, further blending the mixture by passing it through a comminuting machine with knives forward, returning the blended powder to the mixer, adding the talc, blending thoroughly and filling into hard shell gelatin capsules on a capsulating machine.

EXAMPLE G

Suppositories each containing 0.010 g of 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride, 1.245 g of WECOBEE M (a refined synthetic cocoa butter, coconut derived) and 0.045 g of carnauba wax and each having a total weight of 1.3 g were manufactured by melting the WECOBEE M and the carnauba wax in a suitable size glass-lined container, mixing the melt well, cooling it to 45°C, adding the active material

(reduced to a fine powder with no lumps), stirring the mixture until the active material was completely and uniformly dispersed, pouring the mixture into suppository moulds to yield suppository dosage forms having an individual weight of 1.3 g, cooling the suppositories and removing them from the moulds; the suppositories were individually wrapped in wax paper for packaging.

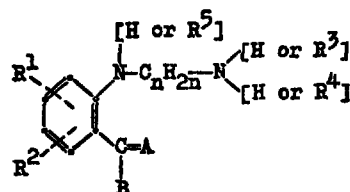
EXAMPLE H

A dosage form of 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride suitable for parenteral use was prepared by filling 50 mg of parenteral grade 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride (fibre free) into a 5 ml ampoule utilising an electric filler, sealing the ampoule and sterilizing it at 124°C for 2 hours; immediately before use, the powder is solubilized with 5 ml of water for injection.

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patent No. 1,056,423.

WHAT WE CLAIM IS:—

1) Compounds of the general formula



wherein A represents an oxygen atom or an =NH, =N—OH or =N—(lower alkyl) group, B represents a pyridyl, phenyl, halo-phenyl, trifluoromethyl-phenyl, nitro-phenyl, (lower alkyl)-phenyl, (lower alkylamino)-phenyl or (lower alkoxy)-phenyl group, R¹ and R² each represent a halogen atom or the trifluoromethyl, nitro or amino group or a lower-alkyl or lower-alkoxy group, R³ and R⁴ each represent a lower-alkyl group or R³ and R⁴ taken together with the nitrogen atom to which they are attached represent a five-membered or six-membered heterocyclic ring which can optionally contain an oxygen atom or a further nitrogen atom [which latter atom may carry as a substituent a lower-alkyl, hydroxy-(lower alkyl), (lower alkoxy)-(lower alkyl) or (lower alkenyloxy)-(lower alkyl) group], R⁵ represents a lower-alkyl or lower-alkenyl group and C_nH_{2n} represents a straight-chain or branched-chain alkylene group in which n stands for 2, 3, 4, 5, 6 or 7 (at least one of R³ and R⁴ being present when

then individually wrapped in wax paper for packaging.

EXAMPLE D

A dosage form of 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride suitable for parenteral use was manufactured by filling 50 mg of parenteral grade 5 - chloro - 2 - [N - (3 - dimethylamino - propyl) - amino] - 2' - fluoro - benzophenone hydrochloride (fibre-free) into a 5 ml ampoule utilizing an electric filler, sealing the ampoule and sterilizing it at 124°C for 2 hours; immediately before use, the powder is solubilized with 5 ml of water for injection.

EXAMPLE E

Tablets each containing 25 mg of 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride, 72 mg of lactose (spray dried), 2 mg of corn starch and 1 mg of calcium stearate and each having a total weight of 100 mg were manufactured by blending the active material, lactose, corn starch and calcium stearate in a suitable mixer, compressing the mixed powder on a heavy-duty tablet compressing machine to yield tablet slugs of ca 30 mm thickness, passing the tablet slugs through a suitable comminuting machine to yield granules with a minimum of fines and recompressing the granulate on a tablet compressing machine using a 6 mm standard concave punch to an average tablet weight of 100 mg.

EXAMPLE F

Capsules each containing 5 mg of 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride, 163 mg of lactose, 37 mg of corn starch and 5 mg of talc and each having a total net weight of 210 mg were manufactured by mixing the active material with the lactose and the corn starch in a suitable mixer, further blending the mixture by passing it through a comminuting machine with knives forward, returning the blended powder to the mixer, adding the talc, blending thoroughly and filling into hard shell gelatin capsules on a capsulating machine.

EXAMPLE G

Suppositories each containing 0.010 g of 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride, 1.245 g of WECOBEE M (a refined synthetic cocoa butter, coconut derived) and 0.045 g of carnauba wax and each having a total weight of 1.3 g were manufactured by melting the WECOBEE M and the carnauba wax in a suitable size glass-lined container, mixing the melt well, cooling it to 45°C, adding the active material

(reduced to a fine powder with no lumps), stirring the mixture until the active material was completely and uniformly dispersed, pouring the mixture into suppository moulds to yield suppository dosage forms having an individual weight of 1.3 g, cooling the suppositories and removing them from the moulds; the suppositories were individually wrapped in wax paper for packaging.

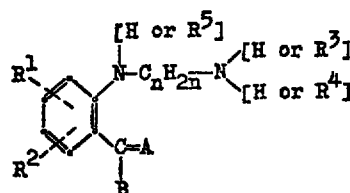
EXAMPLE H

A dosage form of 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) amino] - 2' - fluoro - benzophenone hydrochloride suitable for parenteral use was prepared by filling 50 mg of parenteral grade 5 - chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - 2' - fluoro - benzophenone hydrochloride (fibre free) into a 5 ml ampoule utilizing an electric filler, sealing the ampoule and sterilizing it at 124°C for 2 hours; immediately before use, the powder is solubilized with 5 ml of water for injection.

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patent No. 1,056,423.

WHAT WE CLAIM IS:—

1) Compounds of the general formula



wherein A represents an oxygen atom or an =NH, =N—OH or =N—(lower alkyl) group, B represents a pyridyl, phenyl, halo-phenyl, trifluoromethyl-phenyl, nitro-phenyl, (lower alkyl)-phenyl, (lower alkylamino)-phenyl or (lower alkoxy)-phenyl group, R¹ and R² each represent a halogen atom or the trifluoromethyl, nitro or amino group or a lower-alkyl or lower-alkoxy group, R³ and R⁴ each represent a lower-alkyl group or R³ and R⁴ taken together with the nitrogen atom to which they are attached represent a five-membered or six-membered heterocyclic ring which can optionally contain an oxygen atom or a further nitrogen atom [which latter atom may carry as a substituent a lower-alkyl, hydroxy-(lower alkyl), (lower alkoxy)-(lower alkyl) or (lower alkenyloxy)-(lower alkyl) group], R⁵ represents a lower-alkyl or lower-alkenyl group and C_nH_{2n} represents a straight-chain or branched-chain alkylene group in which n stands for 2, 3, 4, 5, 6 or 7 (at least one of R³ and R⁴ being present when





C_nH_{2n} represents an alkylene group having two carbon atoms between the two nitrogen atoms) and wherein the broken lines denote that the substituents attached thereby are optional, and acid addition salts thereof.

5 2) Compounds as set forth in claim 1, wherein B represents a pyridyl, phenyl, halo-phenyl, trifluoromethyl-phenyl, nitro-phenyl (lower alkyl)-phenyl or (lower alkoxy)-phenyl group, and acid addition salts thereof.

10 3) Compounds as set forth in claim 1, wherein B represents a pyridyl, phenyl, halo-phenyl, trifluoromethyl-phenyl, nitro-phenyl, (lower alkyl)-phenyl or (lower alkoxy)-phenyl group, R^3 and R^4 are both absent and n stands for 3, 4, 5, 6, or 7, and acid addition salts thereof.

20 4) Compounds as set forth in claim 1 or claim 2, wherein R^4 is present, R^5 is absent and C_nH_{2n} stands for a propylene group, and acid addition salts thereof.

25 5) Compounds as set forth in claim 1, wherein R^5 is absent and B represents a 2-(lower alkylamino)-phenyl group, and acid addition salts thereof.

30 6) Compounds as set forth in claim 1 or claim 2, wherein R^4 is present, R^3 is absent and C_nH_{2n} stands for an ethylene or 2-(C_1-C_5 alkyl)-ethylene group, and acid addition salts thereof.

35 7) Compounds as set forth in claim 1 or claim 2, wherein R^4 is present, R^3 and R^5 are absent and C_nH_{2n} stands for an ethylene or 2-(C_1-C_5 alkyl)ethylene group, and acid addition salts thereof.

40 8) Compounds as set forth in claim 1, wherein C_nH_{2n} stands for an ethylene or 2-(C_1-C_5 alkyl)-ethylene group and B represents a 2-(lower alkylamino)-phenyl group, and acid addition salts thereof.

45 9) Compounds as set forth in any one of the preceding claims, wherein R^1 is absent and R^2 is present in the 5-position and represents a halogen atom, and acid addition salts thereof.

10) Compounds as set forth in claim 9 wherein said halogen atom is a chlorine atom, and acid addition salts thereof.

50 11) A 5 - halo - 2 - [N - [3 - di(lower alkyl)amino - propyl] - amino] - 2' - fluoro - benzophenone.

12) 5 - Chloro - 2 - [N - (3 - dimethyl-amino - propyl) - amino] - 2' - fluoro - benzophenone.

55 13) A 5 - halo - 2 - [N - [3 - di-lower alkyl)amino - propyl] - amino] - benzophenone.

60 14) A 5 - nitro - 2 - [N - [3 - di(lower alkyl)amino - propyl] - amino] - benzophenone.

15) A 5 - halo - 2 - [N - 2 - methylamino - ethyl] - N - methyl - amino] - benzophenone.

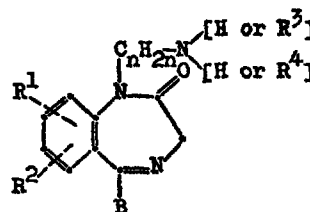
16) 5 - Chloro - 2 - [N - (2 - methylamino - ethyl) - N - methyl - amino] - benzophenone.

17) A 5 - halo - 2 - [N - (2 - ethylamino - ethyl) - amino] - benzophenone. 65

18) 5 - Chloro - 2 - [N - (2 - ethylamino - ethyl) - amino] - benzophenone.

19) A pharmaceutical preparation comprising a compound as set forth in claim 1 or a pharmaceutically acceptable acid addition salt thereof in admixture with a compatible pharmaceutical carrier. 70

20) A process for the manufacture of the diamines claimed in claim 1, which process comprises hydrolysing a benzdiaz[1,4]epine of the general formula 75



wherein B, R^1 , R^2 , R^3 , R^4 , n and the broken lines have the significance given in claim 1, with an acid in the presence of an inert organic solvent and, where required, introducing the group R^5 by lower-alkylation or lower-alkenylation, introducing the group(s) R^3 and/or R^4 by lower-alkylation, converting the resulting product in which A represents an oxygen atom into a corresponding product in which A represents an $=NH$, $=N-OH$ or $=N-(lower\ alkyl)$ group by treatment with ammonia, hydroxy amine or a lower-alkyl amine as the case may require, converting any fluoro-phenyl group B into a (lower alkylamino)-phenyl group, hydrolysing any imine product with a strong acid and/or converting any product into an acid addition salt. 80 85 90 95

21) A process as set forth in claim 20, wherein a benzdiaz[1,4]epine in which B represents a pyridyl, phenyl, halo-phenyl, trifluoromethyl-phenyl, nitro-phenyl, (lower alkyl)-phenyl or (lower alkoxy)-phenyl group is used as the starting material. 100

22) A process as set forth in claim 20 or claim 21, wherein a benzdiaz[1,4]epine in which R^4 is present and C_nH_{2n} stands for a propylene chain is used as the starting material. 105

23) A process as set forth in claim 20 or claim 21, wherein a benzdiaz[1,4]epine in which R^3 is absent, R^4 is present and C_nH_{2n} stands for an ethylene or 2-(C_1-C_5 alkyl)-ethylene chain is used as the starting material. 110

24) A process as set forth in claim 21, wherein a benzdiaz[1,4]epine in which B represents a 2-fluoro-phenyl group is used as the starting material. 115

25) A process as set forth in any one of



claims 20 to 24 inclusive, wherein a benz-
diaz[1,4]epine in which R¹ is absent and R²
is present in the 7-position and represents a
halogen atom is used as the starting material.

5 26) A process as set forth in claim 25,
wherein said halogen atom is a chlorine atom.

27) A process as set forth in claim 25,
wherein a 7 - halo - 1 - [3 - di(lower alkyl)-
amino - propyl] - 5 - (2 - fluoro - phenyl) -
10 2,3 - dihydro - 1H - benzdiaz[1,4] - epinone -
(2) is used as the starting material.

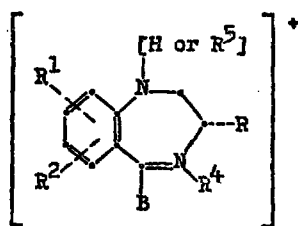
28) A process as set forth in claim 27,
wherein 7 - chloro - 1 - (3 - dimethylamino -
propyl) - 5 - (2 - fluoro - phenyl) - 2,3 - di-
15 hydro - 1H - benzdiaz[1,4] - epinone - (2) is
used as the starting material.

29) A process as set forth in claim 25,
wherein a 7 - halo - 1 - (3 - di(lower alkyl)-
amino - propyl) - 5 - phenyl - 2,3 - dihydro -
20 1H - benzdiaz[1,4]epinone - (2) is used as
the starting material.

30) A process as set forth in claim 20
or claim 21, wherein a 7 - nitro - 1 - [3 -
3 - dhydro - 1H - benzdazi
25 di(lower alkyl) - amino - propyl] - 5 -
phenyl - 2,3 - dihydro - 1H - benzdiaz -
[1,4]epinone - (2) is used as the starting
material.

31) A process as set forth in any one of
30 claims 20 to 30 inclusive, wherein the hydro-
lysis is carried out using hydrochloric acid.

32) A process for the manufacture of the
diamines claimed in claim 1 in which C_nH_{2n}
stands for an ethylene or 2-(C₁-C₅ alkyl)-
35 ethylene group, R⁴ is present and R³ (when
present) represents a lower-alkyl group, which
process comprises treating a quaternary salt
containing a cation of the general formula



40 wherein B, R¹, R², R⁴, R⁵ and the broken lines
have the significance given in claim 1 and R
represents a C₁-C₅ alkyl group, with a base
under hydrolysing conditions, and, where re-
45 quired, introducing the group R⁵ by lower-
alkylation or lower-alkenylation, introducing
the group R³ by lower-alkylation, converting
the resulting product in which A represents
an oxygen atom into a corresponding product
in which A represents an =NH, =N-OH
50 or =N-(lower alkyl) group by reaction with
ammonia, hydroxyl amine or a lower-alkyl

amine as the case may require, converting
any fluoro-phenyl group B into a (lower
alkylamino)-phenyl group, hydrolysing any
imine product with a strong acid and/or con-
55 verting any product obtained into an acid
addition salt.

33) A process as set forth in claim 32,
wherein a quaternary salt in which B repre-
sents a pyridyl, phenyl, halo-phenyl, tri-
60 fluoromethyl-phenyl, nitro-phenyl, (lower
alkyl)-phenyl or (lower alkoxy)-phenyl group
is used as the starting material.

34) A process as set forth in claim 32
or claim 33, wherein a quaternary salt in
which R⁶ is absent is used as the starting
65 material.

35) A process as set forth in claim 33 or
claim 34, wherein a quaternary salt in which
B represents a 3-fluoro-phenyl group is used
70 as the starting material.

36) A process as set forth in any one of
claims 32 to 35 inclusive, wherein a quater-
nary salt in which R¹ is absent and R² is
present in the 7-position and represents a
75 halogen atom is used as the starting material.

37) A process as set forth in claim 36,
wherein said halogen atom is a chlorine atom.

38) A process as set forth in claim 36,
wherein a 7 - halo - 5 - phenyl - 1,4 - di-
80 methyl - 2,3 - dihydro - 1H - benzdiaz-
[1,4]epinium methosulphate is used as the
starting material.

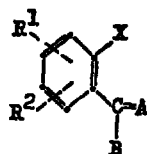
39) A process as set forth in claim 38,
wherein 7 - chloro - 5 - phenyl - 1,4 - di-
85 methyl - 2,3 - dihydro - 1H - benzdiaz-
[1,4]epinium methosulphate is used as the
starting material.

40) A process as set forth in claim 37,
wherein 7 - chloro - 5 - phenyl - 4 - ethyl -
90 2,3 - dihydro - 1H - benzdiaz[1,4]epinium
iodide is used as the starting material.

41) A process as set forth in claim 37,
wherein 7 - chloro - 5 - (2 - fluoro - phenyl) -
4 - ethyl - 2,3 - dihydro - 1H - benzdiaz-
95 [1,4]epinium iodide is used as the starting
material.

42) A process as set forth in any one of
claims 32 to 41 inclusive, wherein the hydro-
lysis is carried out using sodium hydroxide.

43) A process for the manufacture of the
diamines claimed in claim 1, which process
comprises reacting a compound of the general
100 formula



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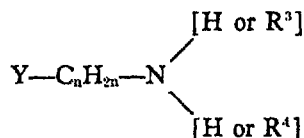
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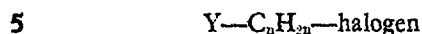
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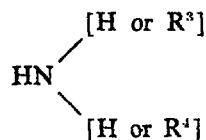
either with a compound of the general formula



or with a compound of the general formula



and treating the reaction product with a compound of the general formula



and, in either case, splitting off any protecting group present and, where required, introducing the group R^2 by lower-alkylation or lower-alkenylation, introducing R^3 and/or R^4 by lower-alkylation, converting any product in which A represents an oxygen atom into a corresponding product in which A represents an $=\text{NH}$, $=\text{N}-\text{OH}$ or $=\text{N}-$ (lower alkyl) group by treatment with ammonia, hydroxyl amine or a lower-alkyl amine as the case may require, converting any fluoro-phenyl group B into a (lower alkylamino)-phenyl group, hydrolysing any imine product with a strong acid and/or converting any product into an acid addition salt; A, B, R^1 , R^2 , R^3 , R^4 , R^5 , n and the broken lines having the significance given in claim 1 and one of the symbols X and Y standing for a halogen atom and the other symbol standing for an amino, lower alkyl-amino, lower alkenyl-amino or protected-amino group.

30 44) A process as set forth in claim 43, wherein a compound of the formula first written in that claim in which B represents a pyridyl, phenyl, halo-phenyl, trifluoromethyl-phenyl, nitro-phenyl, (lower alkyl)-phenyl or (lower alkoxy)-phenyl group is used as the starting material.

40 45) A process as set forth in claim 43 or claim 44, wherein a compound of the formula first written in claim 43 in which X stands for a halogen atom is reacted with a compound of the formula second written in claim 43 in which R^3 and R^4 are absent and Y stands for an amino group.

45 46) A process as set forth in claim 43 or claim 44, wherein a compound of the formula first written in claim 43 in which X stands for an amino, lower alkyl-amino, lower alkenyl-amino or a protected-amino group is reacted with a compound of the formula third written in claim 43 in which Y stands for a halogen atom, the reaction

product is treated with a compound of the formula fourth written in claim 43 and any protecting group is split off from the resulting product.

55 47) A process as set forth in claim 43 or claim 44, wherein a compound of the formula first written in claim 43 in which X represents a protected amino group is reacted with a compound of the formula second written in claim 43 in which Y represents a chlorine, bromine or iodine atom and the protecting group is split off from the reaction product by heating in the presence of a proton-donating acid agent.

60 48) A process as set forth in claim 43 or claim 44, wherein the compound of the second formula written in claim 43 is one in which R^4 is present and C_nH_{2n} represents a propylene group.

65 49) A process as set forth in claim 43 or claim 44, wherein the compound of the formula written in claim 43 is one in which R^4 is present, R^3 is absent and C_nH_{2n} represents an ethylene or 2-(C_1-C_n alkyl)-ethylene group.

70 50) A process as set forth in claim 44, wherein a compound of the formula first written in claim 43 in which B represents a 3-fluoro-phenyl group is used as the starting material.

75 51) A process as set forth in claim 43 or claim 44, wherein a compound of the formula first written in claim 43 in which X stands for a tosyl-amino group is reacted with a compound of the formula second written in claim 43 in which Y stands for a halogen atom.

80 52) A process as set forth in any one of claims 43 to 51 inclusive, wherein the compound of the formula first written in claim 43 R^1 is absent and R^2 is present in the 5-position and represents a halogen atom.

85 53) A process as set forth in claim 52 wherein said halogen atom is a chlorine atom.

90 54) A process as set forth in claim 43 or claim 44, wherein a 5 - halo - 2 - [(3 - halo - propyl) - amino] - 2' - fluoro - benzophenone is treated with a di(lower alkyl)-amine.

95 55) A process as set forth in claim 43 or claim 44, wherein 5 - chloro - 2 - [(3 - chloro - propyl) - amino] - 2' - fluoro - benzophenone is treated with dimethyl amine.

100 56) A process as set forth in claim 43 or claim 44, wherein a 5 - halo - 2 - [(3 - halo - propyl) - amino] - benzophenone is treated with a di(lower alkyl)amine.

105 57) A process as set forth in claim 43 or claim 44, wherein a 5 - nitro - 2 - [(3 - halo - propyl) - amino] - benzophenone is treated with a di(lower alkyl)amine.

110 58) Processes for the manufacture of the diamines claimed in claim 1, substantially as described with reference to Examples 1 to 24.

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59) Diamines as set forth in claim 1, when
manufactured by the process claimed in any
one of claims 20 to 58 inclusive.

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